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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/586,235	HASAN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed December 3, 2001 in Paper No. 12 is acknowledged and has been entered. Claims 7, 8, 10, 13, and 16 have been amended.

2. The declaration under 37 CFR § 1.132 by Bernard Ortel, which was filed August 27, 2001 in Paper No. 10, is acknowledged and has been entered.

3. Claims 1-17 are pending in the application and are currently under prosecution.

Response to Amendment

4. Applicants' arguments with respect to the grounds of rejection set forth in the Office action mailed February 27, 2001 (Paper No. 5) have been considered but are moot in view of the new grounds of rejection that are set forth below.

For clarity of record, the objection to the declaration set forth in the Office action mailed February 27, 2001 is withdrawn. The declaration filed November 22, 2000 in Paper No. 3 complies with the requirements set forth under 37 CFR § 1.67(a).

New Grounds of Objection

Drawings

5. The informal drawings, more particularly the photographs that are labeled Figures 4 and 5 are not of sufficient quality to permit examination.

Accordingly, new drawings are required in reply to this Office action. Applicants are given the same period of time within which to reply to this Office action to submit new drawings. Failure to timely submit new drawings will result in **ABANDONMENT** of the application.

Sp cification

6. The use of the numerous trademarks has been noted in this application. Each letter of a trademark should be capitalized or otherwise the trademark should be

demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

For example, the improper use of "Liazal™" is noted on page 18; the trademark should be demarcated as "Liazal™" or alternatively as "LIAZAL" and followed in parentheses by generic nomenclature.

7. The specification is objected to because of the following informalities:

(a) "Quadra" is misspelled on page 12 in line 8.

(b) "Troglitazone" is misspelled on page 7 in line 6.

(c) The specification recites "CLSM" on pages 21 and 22, but it appears that the acronym is not defined in the disclosure and it cannot be determined to what matter the acronym refers.

Appropriate corrections are required.

Claim Objections

8. Claims 1-13 and 17 are objected to because of the following informalities:

(a) Claims 1-13 and 17 are objected to because claim 1 recites "a PS" in parentheses wherein the claim should only recite "PS".

(b) Claims 1-13 and 17 are objected to because claim 1 recites, "thereby *the* treating unwanted cell proliferation" (italics added for emphasis) and is accordingly grammatically incorrect.

(c) Claim 7 is objected to because the claim is incorrectly punctuated. The comma following "PS" in the last line is unnecessary and its presence causes ambiguity.

(d) Claim 11 is objected to because the claim is incorrectly punctuated. The comma following "compound" in line 2 is unnecessary and its presence causes ambiguity.

(e) Claim 12 is objected to because the claim recites, "unwanted proliferation of prostate cells prostate carcinoma"

(f) Claim 12 is objected to because the claim is incorrectly punctuated. The comma following "hormonal agent" in line 2 is unnecessary and its presence causes ambiguity.

Appropriate corrections are required.

9. Claim 6 is objected to under 37 CFR § 1.75 as being a duplicate of claim 3.

10. Claim 17 is objected to under 37 CFR § 1.75 as being a duplicate of claim 9.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a subject diagnosed with androgen-dependent prostate cancer, wherein said method comprises administering to said subject an agent that induces differentiation of prostate epithelial cells and further comprises administering 5-aminolevulinic acid to the subject, does not reasonably provide enablement for a method for treating a subject having unwanted cell proliferation comprising inducing differentiation in a cell and providing said cell with a photosensitizer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification provided in the disclosure is not reasonably commensurate with the scope of the claims and insufficient to enable the skilled artisan to practice the claimed invention with a reasonable expectation of success without the need to perform additional, undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

LNCaP is an androgen-responsive prostate cancer cell line. The specification teaches that more protoporphyrin accumulates in LNCaP cells treated with the synthetic androgen R1881 than in cells not so treated following exposure of the cells to δ-aminolevulinic acid (ALA). Furthermore, the specification teaches that following exposure to ALA and subsequent irradiation of the cells, the survival of the R1881-pretreated cells is decreases relative to the survival of cells not so pretreated.

The declaration under 37 CFR § 1.132 by Dr. Ortel, which was filed August 27, 2002 in Paper No. 10, states that the combination of differentiation therapy and photodynamic therapy more effectively reduces the tumor burden of mice than either therapy alone. More particularly, the declaration states that mice bearing subcutaneous mouse EMT6 mammary sarcomas were pretreated with all-*trans*-retinoic acid (ATRA) and responded better to treatment with ALA than mice not so pretreated.

The claims, however, are drawn to a method for treating a subject having unwanted cell proliferation. Although the specification exemplifies a subject having an unwanted cell proliferation as a patient having a tumor, broadly interpreted, the claims encompass a method for treating a subject that is obese and who desires, for example, to reduce the proliferation of his or her adipocytes. The teachings of the specification cannot be extrapolated to the enablement of a method for treating an obese patient as there is no evidence that would suggest a method comprising inducing the

differentiation of a cell, providing the cell with a photosensitizer, and activating the photosensitizer can effectively ameliorate the subject's obesity. The art is unpredictable in nature; and one skilled in the art would not accept the assertion that the claimed invention can be used successfully without need of performing additional, undue experimentation based only upon the disclosure that LNCaP cells that have been pretreated with R1881 are more sensitive to irradiation after exposure to ALA than LNCaP cells not so pretreated.

While the declaration under 37 CFR § 1.132 by Dr. Ortel states that the combination of differentiation therapy and photodynamic therapy is more effective than either therapy alone, the showings are limited to studies of an androgen-responsive prostate cancer cell line and a transplantable mammary sarcoma and are therefore not reasonably commensurate in scope with the claims. For example, the declaration does not, nor does the specification provide a showing that the invention can be practiced to successfully treat a subject having an androgen-independent prostate cancer, which is not responsive to treatment with androgen. One skilled in the art would not expect the combination of differentiation therapy and photodynamic therapy to be more effective than either therapy alone in treating a patient diagnosed with androgen-independent prostate cancer in cases where the patient is treated with androgen, a known differentiating agent, because the cancer would not be expected to respond to androgen treatment and there is no reason to expect that treatment of the cancer with androgen would promote the increased accumulation of photoactive porphyrin in the cells following their exposure to ALA.

Furthermore, claims 7 and 8 specifically encompass a method that further comprises administering to the subject a compound that causes the formation of a photosensitizer. However, the specification does not teach the use of, or exemplify a compound that might be administered to the subject to cause the formation of a photosensitizer *per se*. Accordingly, there is an insufficient amount of guidance, direction, and exemplification to enable the skilled artisan to make and use this particular embodiment of the claimed invention.

Claim 9 is drawn to a method comprising administering to the subject a photosensitizer that is coupled to a targeting moiety, such as an antibody. However this embodiment of the claimed invention is not exemplified.

With regard to targeted therapy, Vitetta, et al (*Cancer Research* **54**: 5301-5309, 1994) teach that "despite [...] intellectual appeal, the general therapeutic efficacy of tumor-reactive MAbs [monoclonal antibodies] has been disappointing. In particular the results of clinical studies in patients with solid tumors showed little efficacy, except in the setting of minimal disease" (citations omitted) (page 5301, column 1). Vitetta, et al continue, teaching that there are a number of significant limitations in their use as first-line therapy for solid tumors page 5305, (columns 1-2):

> Only 0.001 to 0.1% of injected MAb [monoclonal antibody] will localize to each [gram] of tumor mass. Moreover, MAbs, even at high serum concentrations, cannot gain access to all the cells in solid epithelial tumor. The reasons for this are poor and heterogeneous blood supply, the blood-tumor barrier, and the selective binding of the MAb by the tumor cells closest to the blood supply. In addition, MAbs by themselves probably cannot kill the 10^{10}-10^{12} malignant cells that may be necessary to cure a patient with a disseminated tumor (citations omitted) (page 5305, columns 1-2).

Furthermore, the strategic approach to treating cancer using targeted monoclonal antibody therapy is analogous to active specific immunotherapy (e.g., vaccination against tumor-associated antigens), since at least to the extent that the latter theoretically induces a humoral immune response (i.e., the production of tumor-specific antibody). Monoclonal antibody therapy can be defined as passive immunization, cancer vaccine therapy as active immunization. Because the efficacy of both approaches depends upon the effectiveness of tumor antigen-specific antibodies to ameliorate or inhibit tumors, both also share the same or corresponding limitations. Bodey, et al (*Anticancer Research* **20**: 2665-2676, 2000) teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). In the abstract Bodey, et al disclose:

> Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

Thus, it is clear that there is much contention in the art that targeted monoclonal antibody-based therapies are presumed ineffective until proven otherwise, and just as clear, is the lack of predictability that is associated with the art.

Claim 11 is drawn to a method comprising administering to subject an antidiabetic compound, such as troglitazone, or the ligand of a transcription factor. However, these embodiments of the claimed invention are not exemplified. While some antidiabetic compounds, such as troglitazone are peroxisome proliferators and bind the transcription factor PPAR-γ, for example, many other antidiabetic compounds are not. One skilled in the art would not accept the assertion that administering any antidiabetic compound to a subject can increase the effectiveness of photodynamic therapy, or be used in conjunction with a photosensitizer or precursor thereof to successfully treat unwanted cell proliferation. For example, there is no evidence of record that would suggest that insulin, or a sulfonylurea compound, such as glimepiride, or any other antidiabetic that acts by a mechanism different from that of troglitazone would increase the sensitivity of unwanted cells to photodynamic therapy. Moreover, there is no evidence of record that would suggest that administering any other ligand of any other transcription factor could be used in conjunction with a photosensitizer to rid the subject of unwanted cells. The activation of a transcription factor that does not regulate differentiation, for example, would not be expected to increase the accumulation of the photosensitizer in a cell; and one skilled in the art would not accept the assertion that any antidiabetic compound or any ligand of any transcription factor can be used in

practicing the claimed invention to successfully eradicate or ameliorate a condition characterized by unwanted cell proliferation.

Claim 12 is drawn to a method comprising administering a hormonal agent to the patient in conjunction with a photosensitizing agent. While the specification teaches that the synthetic androgen R1881 increases the amount of protoporphyrin that accumulates in LNCaP cells, it is known that other hormonal agents fail to have the same effect. For example, Momma, et al (International Journal of Cancer 72: 1062-1069, 1997) teaches that while dihydrotestosterone, like R1881 increases the cellular content of protoporphyrin, but another hormonal agent, namely estradiol fails to do so. Other hormonal agents are equally as unlikely to be effective in treating a patient diagnosed with prostate cancer. Therefore, it is evident that the claimed method cannot be practiced with a reasonable expectation of success without need to perform additional, undue experimentation to determine whether or not a particular hormonal agent can be used effectively.

Otherwise, claim 12 is drawn to a method comprising administering in conjunction with a photosensitizing agent, an unspecified agent to the patient that increases the level of retinoic acid in an unspecified reservoir. However, this method is not exemplified in the specification, and it is not immediately apparent which agents might be used in practicing this particular embodiment of the invention.

In addition, the claims encompass the use of a rather broad genus of photosensitizers and precursors thereof; yet the specification only demonstrates the use of a single precursor of a photosensitizer, namely ALA. In addition, it is noted that the showing provided in the declaration under 37 CFR § 1.132 by Dr. Ortel is no more extensive, since again only the use of ALA is described therein. If the mechanism by which a differentiating agent causes increased accumulation of protoporphyrin in cells induced to differentiate relative to control cells involved the increased expression of ferrochelatase, an enzyme that participates in the conversion of ALA into protoporphyrin, it is possible that some photosensitizing agents or precursors thereof will not accumulate preferentially in differentiating cells because the uptake and/or conversion of some may not be dependent upon the enzyme. Absent a showing that is

reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that the level of any photosensitizer will accumulate in a cell upon the induction of differentiation.

Finally, one cannot extrapolate the teachings of the specification to the enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with the claims, because it is well known that the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura, like Bodey, et al (cited *supra*), discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Although the teachings of Bergers, et al (*Current Opinion in Genetics and Development* **10**: 120-127, 2000) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger, et al. Bergers, et al teach, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers, et al, disclose that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers, et al comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the

drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers, et al also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering a pharmaceutical composition or a combination of such compositions purported to have a desired pharmacological effect to a subject. Always the efficacy of any unproven drug regimen must be determined empirically. Therefore, in such an unpredictable art as this, the disclosure of such empirical determinations (i.e., working exemplification) must be commensurate in scope with its expected and indicated uses if the specification is to be considered enabling; otherwise, in the absence of sufficient exemplification, the skilled artisan would have to perform undue experimentation to practice the claimed invention with a reasonable expectation of success.

In summary, the amount of guidance, direction, and exemplification that is disclosed in the specification is insufficient to enable the skilled artisan to have a reasonable expectation of successfully practicing the claimed invention without having need to perform additional, undue experimentation. Furthermore, neither the specification nor the declaration provide a showing of evidence that is reasonably commensurate in scope with the claims. Upon consideration of the state of the art and in particular, the level of unpredictability associated with the art, in the absence of exemplification that is reasonably commensurate in scope with the claims, the specification fails to meet the enablement requirement set forth under 35 USC § 112, first paragraph.

13. Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for detecting a cell characterized as having unwanted proliferation. While it is unclear how a cell can be characterized as having unwanted proliferation, it is noted that the invention is not exemplified. Furthermore,

while it is unclear which difference in the cell having unwanted proliferation and a control cell is to be detected in practicing the invention, or whether such a difference is qualitative or quantitative, one skilled in the art would not accept the assertion that detecting any difference between a cell and a control cell would enable the identification of the former.

In addition, it would appear that if, for example, a difference in the amount of protoporphyrin that accumulates in a cell having unwanted proliferation and a control cell were to be detected, the differentiating agent would necessarily have to have disparate effects upon the cell having unwanted proliferation and the control cell. Otherwise, one would not expect the amount of protoporphyrin that accumulates in the cell having unwanted proliferation to be different from that which accumulates in the control cell. However, there is no evidence of record that would suggest that a control cell would be disparately affected by exposure to a differentiating agent relative to a cell having unwanted proliferation. Furthermore, there is no evidence that any fluorescent compound (e.g., fluorescein) will be differentially taken up by a cell having unwanted proliferation following exposure to a differentiation agent relative to a control cell treated in the same manner. Accordingly, in the absence of exemplification and/or a more sufficient amount of guidance and direction, the skilled artisan could not practice the claimed invention with a reasonable expectation of success without having need to perform additional, undue experimentation.

14. Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 11 is drawn to a method for treating a subject having a condition characterized by unwanted cell proliferation. According to the limitations of claim 11, the method comprises administering to the subject an antidiabetic compound or the ligand of a transcription factor.

The disclosure is not sufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph. Although the disclosure includes an example of an antidiabetic compound, namely troglitazone, which is incidentally a ligand for the transcription factor PPAR-γ, the specification fails to set forth a representative number of either antidiabetic compounds or ligands for transcription factors that can be used in practicing the claimed invention. Moreover, the specification fails to describe the characteristics or features of either the antidiabetic compounds or ligands for transcription factors that are common among at least a substantial number of the members of these genera. In other words, there is indication as to how troglitazone is to be considered representative of either genus.

Claim 12 is drawn to a method for treating a subject having a condition characterized by unwanted cell proliferation. According to the limitations of claim 12, the method comprises administering to the subject a hormonal agent or an agent that increases levels of retinoic acid.

Here again, the disclosure is not sufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph. Although the disclosure exemplifies the use of a hormonal agent, namely R1881, the specification fails to set forth a representative number of either hormonal agents or agents that can be used to increase the level of retinoic acid, which can be used in practicing the claimed invention. Moreover, the specification fails to describe the characteristics or features of either the hormonal agents or agents that can be used to increase the level of retinoic acid, which are common among at least a substantial number of the members of these genera. While the specification includes the glucocorticoids as an example of a hormone that might be used to practice the invention, there is indication as to how R1881 and the glucocorticoids are related to one another or considered representative of the genus of hormonal agents to which the claims refer.

Accordingly, one skilled in the art would not be capable of recognizing or distinguishing those compounds, ligands, or agents that are considered useful in practicing the claimed invention, and which are not. Furthermore, due to the insufficiency of the written description, the specification would not reasonably convey to

the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 are indefinite because claims 1, 2, 12, and 14 recite the term "unwanted". The term unwanted is a subjective term; what may be considered "unwanted" by one person, may not be considered so by another. Accordingly, the metes and bounds of the invention are not sufficiently delineated by the claim to meet the requirements set forth under 35 USC § 112, second paragraph.

Claim 12 is vague and indefinite because the claim recites the limitation "which increases levels of retinoic acid". Recitation of the limitation renders the claim vague and indefinite because it cannot be ascertained where the levels of retinoic acid are to be increased by administering the agent to the subject. Furthermore, recitation of the limitation renders the claim vague and indefinite because it cannot be ascertained to what degree the agent must increase the level of retinoic acid, and the specification fails to provide a standard by which the requisite amount of increase might be ascertained. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 14-16 are vague and indefinite because claim 14 recites the limitation "characterized as having unwanted proliferation". Recitation of the limitation renders the claim vague and indefinite because it is unclear how the claim requires the cell to be "characterized" as having unwanted proliferation. Moreover, it cannot be ascertained how a cell can be characterized as *having unwanted proliferation*. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 14-16 are indefinite because claim 14 recites the step of "detecting a difference between the cell and a control cell", but does not define what difference is to be detected, or how such a difference is to be detected in practicing the invention. Moreover, it cannot be ascertained whether said difference is qualitative or quantitative, but if the latter, it could not be ascertained to what extent the claim would require the cell having unwanted proliferation to be different from the control cell. In addition, the specification does not appear to provide a standard for ascertaining the requisite degree of difference. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 14-16 are indefinite because claim 14 does not recite a positive process step that clearly relates back to the preamble of the claim. The preamble recites, "[a] method for detecting a cell" while the process step recites, "thereby detecting the presence of a disorder". Accordingly, it is unclear whether the claim is drawn to a method for detecting a cell, or rather a method for detecting a disorder. Consequently, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

19. Claims 1-3, 6, 7, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Koulu (*Photodermatology* **1**: 42-43, 1984).

Claims 1-3, 6, 7, and 13 are drawn to a method comprising inducing differentiation in a cell, providing the cell with a photosensitizer by administering the photosensitizer to a patient, and activating the photosensitizer.

Koulu teaches a method comprising administering a differentiating agent, namely a retinoid to a patient having psoriasis, administering a photosensitizer, namely psoralen to the patient, and irradiating the patient.

20. Claims 1, 2, and 13-15 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,784,162-A.

Claims 1, 2, and 13 are drawn to a method comprising inducing differentiation in a cell, providing the cell with a photosensitizer, and activating the photosensitizer. Claims 14 and 15 are drawn to a method comprising providing a differentiating agent to a cell of a subject, providing a light-emitting agent to the cell, activating the agent, and detecting a difference between the cell and a control cell.

US Patent No. 5,784,162-A ('162) teaches a method comprising inducing differentiation in a cell, providing the cell with a photosensitizer, and activating the photosensitizer (columns 45-48, Example 3). Briefly, '162 teaches that cells of a subject can be treated with dimethylsulfoxide (DMSO), a known differentiating agent, which can then be treated with 5-aminolevulinic acid (ALA), a known photosensitizing agent, and exposed to light. In Example 8 (columns 58-61), '162 illustrates a method for detecting an abnormal cell comprising providing a light-emitting agent to the cell, activating the agent, and detecting a difference between the cell and a control cell.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1-4, 6-8, and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ortel, et al (*British Journal of Cancer* **77**: 1744-1751, June 1998) and Momma, et al (*International Journal of Cancer* **72**: 1062-1069, 1997) in view of Mueller, et al (*Molecular Cell* **1**: 465-470, 1998), and Santini, et al (*British Journal of Haematology* **102**: 1124-1138, 1998).

Ortel, et al and Momma, et al teach that inducing differentiation augments the intracellular accumulation of protoporphyrin following exposure of cells to 5-aminolevulinic acid (ALA).

Ortel, et al demonstrate that differentiation-inducing pretreatments of keratinocytes causes the increased accumulation of protoporphyrin in the cells following exposure to ALA, which Ortel, et al attribute to an increased uptake of ALA by the cells, a decreased efflux of protoporphyrin by the cells, and an increased synthetic capacity of the cells to produce protoporphyrin. Ortel, et al also demonstrate that following exposure to ALA, other types of cells similarly accumulate protoporphyrin in response to treatment with differentiation agents.

Momma, et al demonstrate that the pretreatment of prostate cancer cells with a differentiating agent, namely 5α-dihydrotestosterone (DHT) results in the increased accumulation of protoporphyrin following exposure of the cells to ALA. Momma, et al disclose that their study provides another example in which the amount of protoporphyrin produced by a cell line does not correlate with the cell line's growth rate. Although Momma, et al does not explicitly state that the increased accumulation of

protoporphyrin in the cells can be attributed to the induction of differentiation, it appears that the increased accumulation cannot be attributed to a growth stimulatory effect. Moreover, Momma, et al disclose that the preferential accumulation of protoporphyrin in differentiating cells might be due to an increase in the level of expression of the gene encoding ferrochelatase, which is an enzyme that participates in the conversion of ALA into protoporphyrin. At the time the invention was made, it was well established that ferrochelatase is a marker of differentiation, as it had been shown that its expression increases during dimethylsulfoxide (DMSO)-induced differentiation of DS-19 murine erythroleukemia (MEL) cells.

Therefore, in view of the teachings of Ortel, et al and Momma, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that differentiating cells accumulate more photosensitizer than non-differentiating cells. As it was widely known in the art that proliferating cells, such as tumor cells preferentially accumulate photosensitizer, the studies of Ortel, et al and Momma, et al provide either a possible mechanistic explanation for this characteristic of tumor cells or a suggestion that during differentiation the preferential accumulation of photosensitizer by tumor cells is further enhanced.

Accordingly, while neither Ortel, et al nor Momma, et al explicitly disclose a method for treating a patient diagnosed with breast cancer, prostate cancer, or a hematopoietic cell malignancy, it would have been *prima facie* obvious to one of ordinary skill in the art to induce the differentiation of the tumor cells before or during treatment with the photosensitizing agent ALA, since both Ortel, et al and Momma, et al teach that during differentiation cells accumulate more protoporphyrin than the cells would otherwise. As it was well established that increased accumulation of photosensitizer within a cell correlates with the cell's sensitivity to irradiation, one of ordinary skill in the art would have been motivated to modify the conventional methods of photodynamic therapy by first or conjunctionally contacting the targeted cells with a differentiating agent.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a differentiating agent that was most

likely to induce the differentiation of the targeted cells. For example, if the patient to be treated had been diagnosed with androgen-responsive prostate cancer, it would have been *prima facie* obvious given the teachings of Momma, et al to use an androgen such as DHT to induce the differentiation of the patient's tumor cells before or during the administration of ALA.

Mueller, et al teach that antidiabetic compounds, namely the thiazolidinediones, such as troglitazone, induce the terminal differentiation of breast cancer cells, while santini, et al teach that treatment of a patient diagnosed with the hematopoietic cell malignancy promyelocytic leukemia with all-*trans*-retinoic acid (ATRA) is the paradigm of differentiation therapy. Accordingly, upon treating a patient diagnosed with a malignancy of the breast, it would have been *prima facie* obvious to one of ordinary skill to use a thiazolidinedione such as troglitazone to induce the differentiation of the patient's tumor cells before or during the administration of ALA. On other hand, upon treating a patient diagnosed with a hematopoietic cell malignancy, it would have been *prima facie* obvious to use a retinoid such as ATRA to induce the differentiation of the patient's tumor cells. One of ordinary skill in the art at the time the invention was made would have been motivated to use a differentiating agent that would cause the targeted cells to differentiate in order to optimize the therapeutic effect.

In addition, because proliferating cells, such as tumor cells, were already known to preferentially take up photosensitizing agents and because the prior art cited herein teaches that differentiating cells accumulate more photosensitizer than control cells, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that inducing the differentiation of tumor cells would provide an even larger difference in the amount of photosensitizer that accumulates in the tumor, cell relative to the control cell, than would be present if differentiation had not been induced. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that following the induction of differentiation, tumor cells would be better distinguished from normal, control cells by the accumulation of a photosensitizer, which would aid in the identification of the tumor cells and diagnosis of a patient upon the histological analysis of a biopsy acquired from the

patient. One of ordinary skill in the art at the time the invention was made would have been motivated to develop a method for identifying tumor cells that capitalizes upon such a distinguishing feature of tumor cells, because improved diagnostic methods had been long sought.

Conclusion

23. No claims are allowed.

24. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent No. 5,145,677-A teaches a method comprising administering to a patient a differentiating agent, namely interferon-γ, which further comprises administering to the patient a photosensitizing agent or differentiating agents other than interferon-γ. US Patent No. 5,594,015-A teaches a method for treating a patient having psoriasis that comprises administering to the patient a thiazolidine derivative. Fujimura, et al teach that troglitazone affects the growth and differentiation of hematopoietic cell lines. Haydon, et al teach various peroxisome proliferators and retinoids that affect the differentiation of cancer cells. US Patent No. 5,981,586-A teaches methods for treating patients diagnosed with a disorder associated with the abnormal proliferation of cells, which comprise administering to the patients a compound that activates PPAR-γ. Esquenet, et al teach that differentiation of prostate cancer cells can be affected by various agents. US Patent Nos. 4,994,491-A, 5,475,006-A, 5,821,254-A, and 5,932,622-A teach therapeutic methods that comprise administering a retinoid to a patient. US Patent Nos. 5,407,808-A and 5,773,460-A teac therapeutic methods that comprise administering a photosensitzer or a combination of agents to a patient.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
October 17, 2002

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